**Appendix A**
**Marked-Up Version of Amendments to Specification**

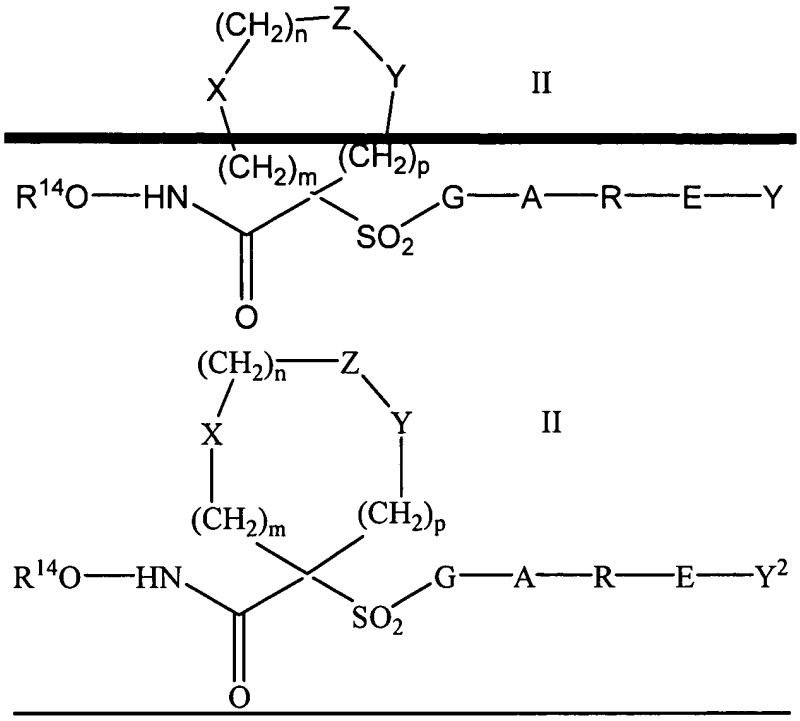
**The paragraph bridging lines 5-18 on page 4 has been amended as follows:**

TNF-α convertase is a metalloprotease involved in the formation of soluble TNF-α. Inhibition of TNF-α convertase (TACE) inhibits production of active TNF-α. Compounds that inhibit both MMPs activity and TNF-α production have been disclosed in WIPO International Publication Nos. WO 94/24140, WO 94/02466 and WO 97/20824. Compounds that inhibit MMPs such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF (Gearing et al., **370 [[376]]**, 555-557 (1994), McGeehan et al., Nature, **370 [[376]]**, 558-561 (1994)). There remains a need for effective MMP inhibitors. There also remains a need for effective TNF-α convertase inhibiting agents.

**The paragraph bridging lines 4-18 on page 6 has been amended as follows:**

Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are known as is shown in, for example, ~~WO95/12389~~ **WO95/13289**, WO96/11209 and U.S. 4,595,700. Hydroxamate group-containing MMP inhibitors are disclosed in a number of published patent applications such as WO 95/29892, WO 97/24117, WO 97/49679 and EP 0 780 386 that disclose carbon back-boned compounds, and WO 90/05719, WO 93/20047, and WO 95/09841 and WO 96/06074 that disclose hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones, as does the article by Schwartz et al., *Progr. Med. Chem., 29*:271-334 (1992) and those of Rasmussen et al., *Pharmacol. Ther., 75(1)*: 69-75 (1997) and Denis et al., *Invest. New Drugs, 15(3)*: 175-185 (1997).

**Formula II at line 4 on page 15 has been amended as follows:**




**The paragraph bridging pages 20 and 21 (*i.e.*, page 20, line 26 to page 21, line 4) has been amended as follows:**

G-A-R-E-$Y^{2}$ is a substituent that preferably has a length greater than that of a pentyl group, and more preferably has a length greater than that of a hexyl group. The substituent G-A-R-E-$Y^{2}$ preferably has a length that is less than that of an icosyl group, and is more preferably less than that of a stearyl group. In this substituent:

**The paragraph bridging lines 23-24 on page 22 has been amended as follows:**

(7) E is absent or R is bonded directly to $Y^{2}$; and

**The paragraph bridging pages 22 and 23 (*i.e.*, page 22, line 25 to page 23, line 10) has been amended as follows:**

$Y^{2}$ is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl,

heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and **[[a]]** aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

**The paragraph bridging lines 20-23, page 23 has been amended as follows:**

m, n, p, X, Z, Y and $R^{14}$ are as defined above for formula II, and the $R^3$ radical that is defined below is a sub-set of the previously discussed G-A-R-E-$Y^2$ substituents.

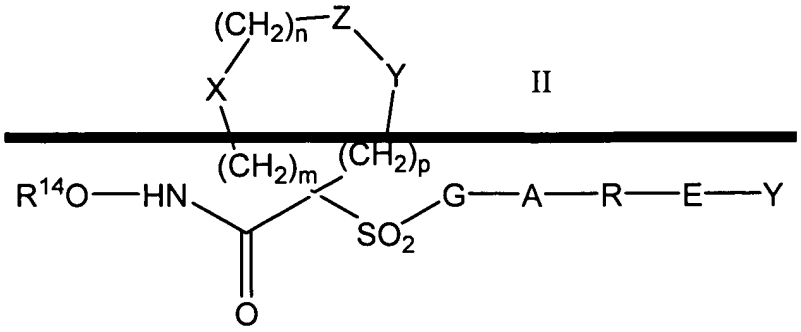
**The paragraph bridging lines 3-6 on page 25 has been amended as follows:**

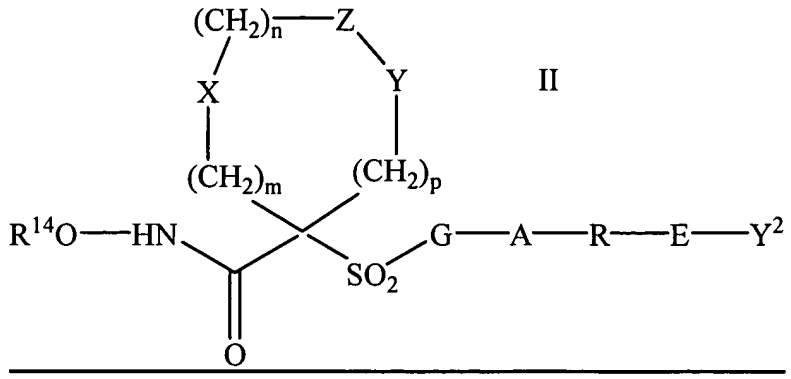
wherein $R^3$ is as defined above for formula I, more preferably as defined for formula II (wherein this $R^3$ group is the G-A-R-E-$Y^2$ substituent), and more preferably still as defined for formula III, and

**The paragraph bridging lines 4-11 on page 27 has been amended as follows:**

wherein m, n, p, X, Z and Y are as defined above for formula II, g is zero, 1 or 2 and $R^{24}$ is $R^3$ as defined in formulas I, III or IV, is the substituent G-A-R-E-$Y^2$ of formula II (formula VIA) or is $R^{3'}$, an aryl or heteroaryl group that is substituted with a coupling substituent reactive for coupling with another moiety (formula VIB), such as a nucleophilically displaceable leaving group, D.

**Formula II at line 19 on page 42 has been amended as follows:**






**The paragraph bridging lines 7-13 on page 48 has been amended as follows:**

G-A-R-E-$Y^{\underline{2}}$ is a substituent that preferably has a length greater than that of a pentyl group, and more preferably has a length greater than that of a hexyl group. The substituent G-A-R-E-$Y^{\underline{2}}$ preferably has a length that is less than that of an icosyl group, and is more preferably less than that of a stearyl group. In this substituent:

**The paragraph bridging lines 4-5 on page 50 has been amended as follows:**

(7) E is absent or R is bonded directly to $Y^{\underline{2}}$; and

**The paragraph bridging lines 6-21 on page 50 has been amended as follows:**

$Y^{\underline{2}}$ is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and **[[a]]** aminoalkyl group, wherein the aryl or heteroaryl or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

**The paragraph bridging pages 50 and 51 (*i.e.*, page 50, line 22 to page 51, line 2) has been amended as follows:**

The substituent -G-A-R-E-$Y^{\underline{2}}$ preferably contains two to four carbocyclic or heterocyclic rings, including the aryl or heteroaryl group, G. More preferably, each of those rings is 6-membered. Additional separate preferences for a compound of formula II include: (a) that A is -O- or -S-, (b) R is an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group, (c) E is absent, and (d) $Y^{\underline{2}}$ is selected from the group consisting of hydrido, an alkyl, alkoxy, perfluoroalkoxy and a perfluoroalkylthio group.

**The paragraph bridging lines 9-13 on page 58 has been amended as follows:**

Here, $R^3$ is as defined above as to Formulas I, III and more preferably as defined as to formula II (wherein the $R^3$ radical is the substituent G-A-R-E-$Y^{\underline{2}}$). Most preferably, $R^3$ is as defined in formula III.

**The paragraph bridging pages 76 and 77 (*i.e.*, page 76, line 26 to page 77, line 4) has been amended as follows:**

$R^{24}$ is $R^3$ as defined in formulas I, III, IV or is the substituent G-A-R-E-$Y^{\underline{2}}$ of formula II (formula VIA). Alternatively, $R^{24}$ is $R^{3'}$, an aryl or heteroaryl group that is substituted with a coupling substituent reactive for coupling with another moiety (formula VIB), such as a nucleophilically displaceable leaving group, D.

**The paragraph bridging lines 7-24 on page 77 has been amended as follows:**

Exemplary nucleophilically displaceable leaving groups, D, include a halo (fluoro, chloro, bromo, or iodo), nitro, azido, phenylsulfoxido, aryloxy, $C_1$-$C_6$-alkoxy, a $C_1$-$C_6$-alkylsulfonate or arylsulfonate group and a trisubstituted ammonium group in which the three substituents are independently aryl, ar-$C_1$-$C_6$-alkyl or $C_1$-$C_6$-alkyl. Additional coupling substituents include, without limitation, a hydroxyl group and an amino group that can be coupled with carbonyl-containing moieties to form esters, urethanes, carbonates, amides and ureas. Similarly, a carboxyl coupling substituent can be used to form an ester, thioester or amide. Thus, a coupling substituent is useful in converting a coupling substituent-containing

aryl or heteroaryl group into a substituent such as a G-A-R-E-$Y^{\underline{2}}$ substituent discussed hereinabove by the formation of a covalent bond.

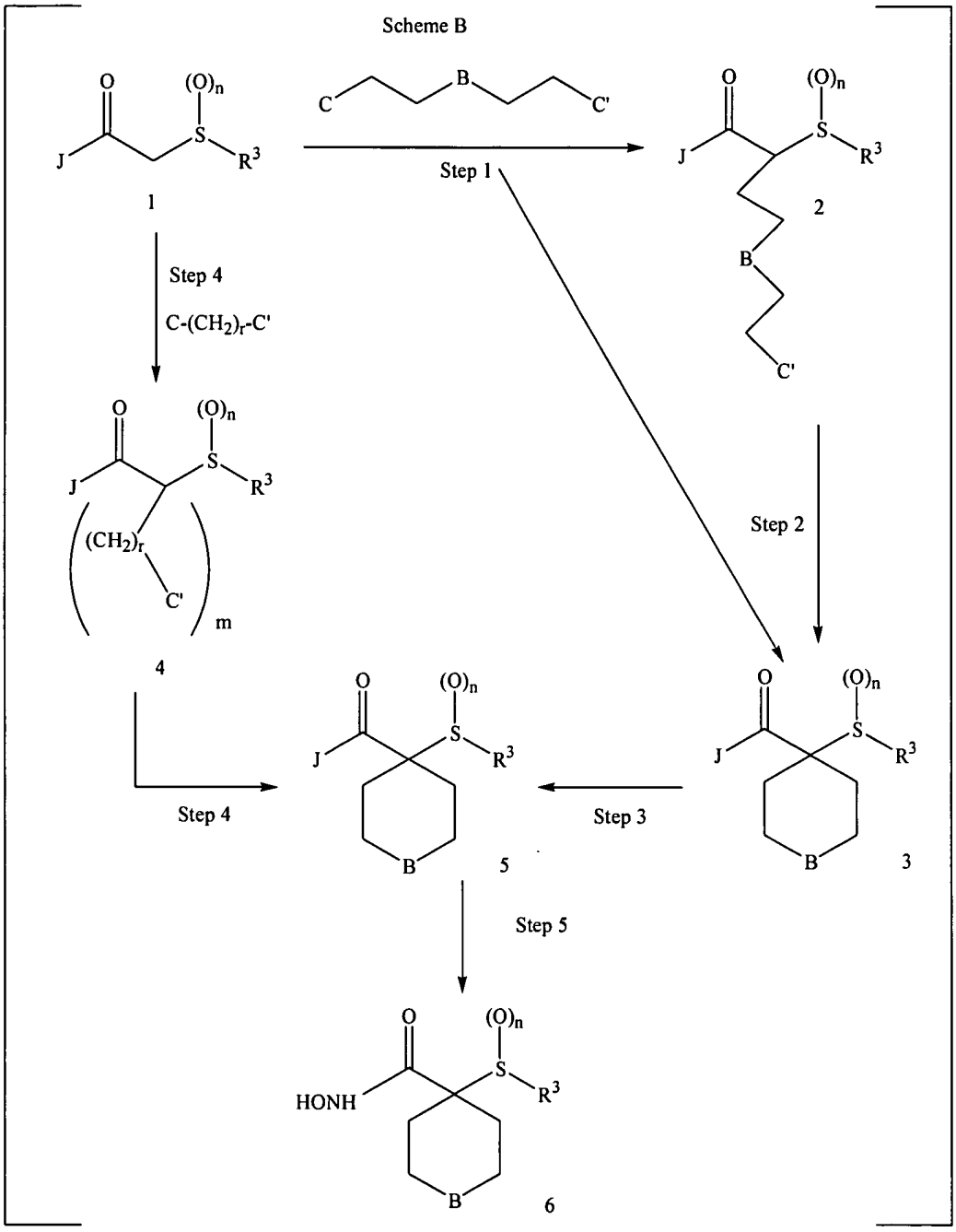
**The paragraph bridging lines 1-8 on page 78 has been amended as follows:**

A compound of formula VI can be coupled with another moiety at the $R^{3'}$ coupling substituent to form a compound whose newly formed $R^3$ group is that of formulas I, III, IV or -G-A-R-E-$Y^{\underline{2}}$. Exemplary of such couplings are the nucleophilic displacement to form ethers and thioethers, as well as the formation of ester, amide, urea, carbonate, urethane and the like linkages.

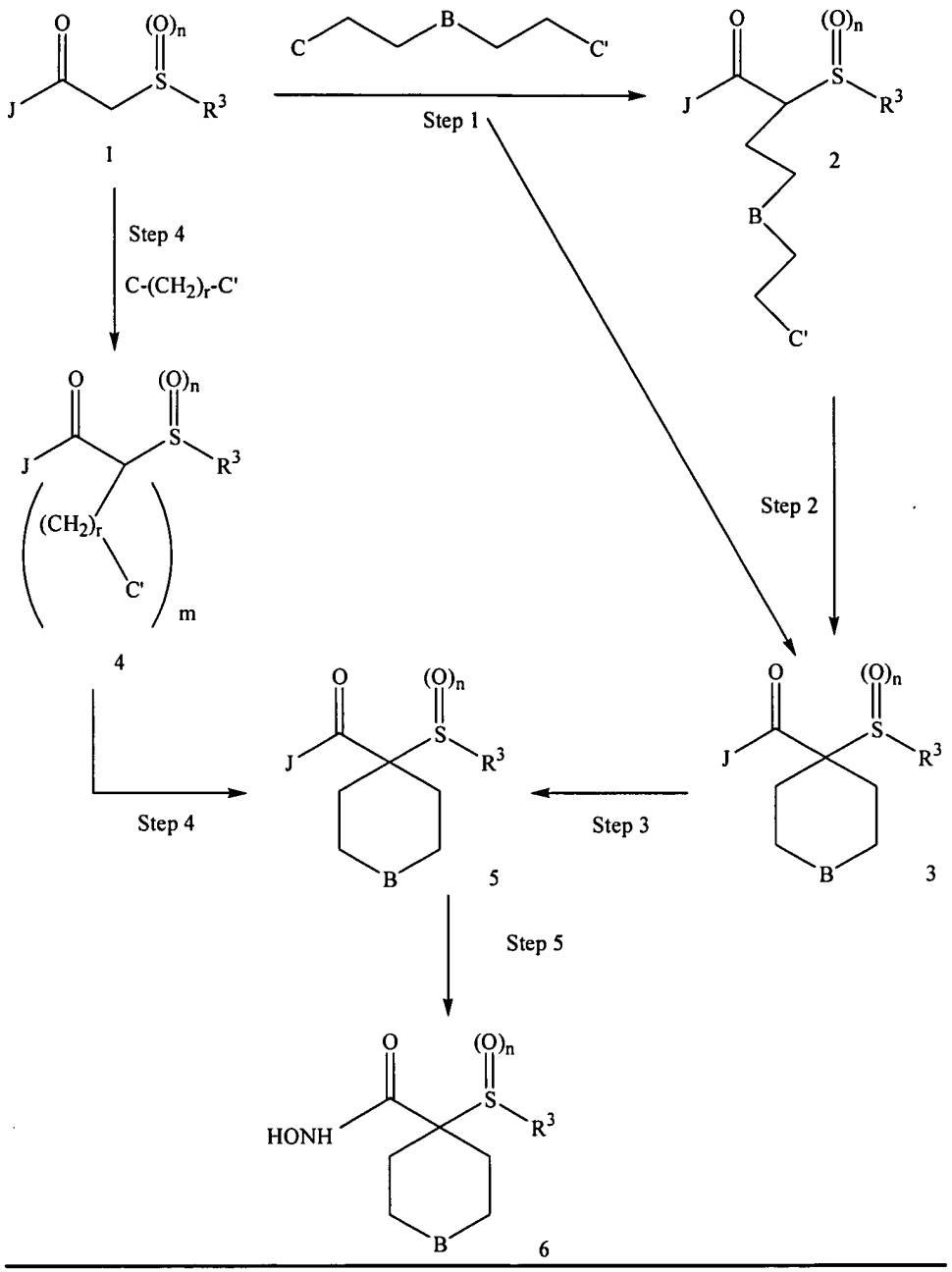
**The paragraph bridging pages 95 and 96 (*i.e.*, page 95, line 30 to page 96, line 5) has been amended as follows:**

The structures in Schemes 1 through 19 are also shown with compounds that represent the other compounds of this invention. The aromatic ring in Scheme C is aryl and heteroaryl. The moieties of -A-R-E-$Y^{\underline{2}}$ are as defined before. Reactions illustrated involving a spiroheterocyclic nitrogen atom may not be applicable to those compounds with sulfur or oxygen.

**Scheme B at line 1 on page 101 has been amended as follows:**

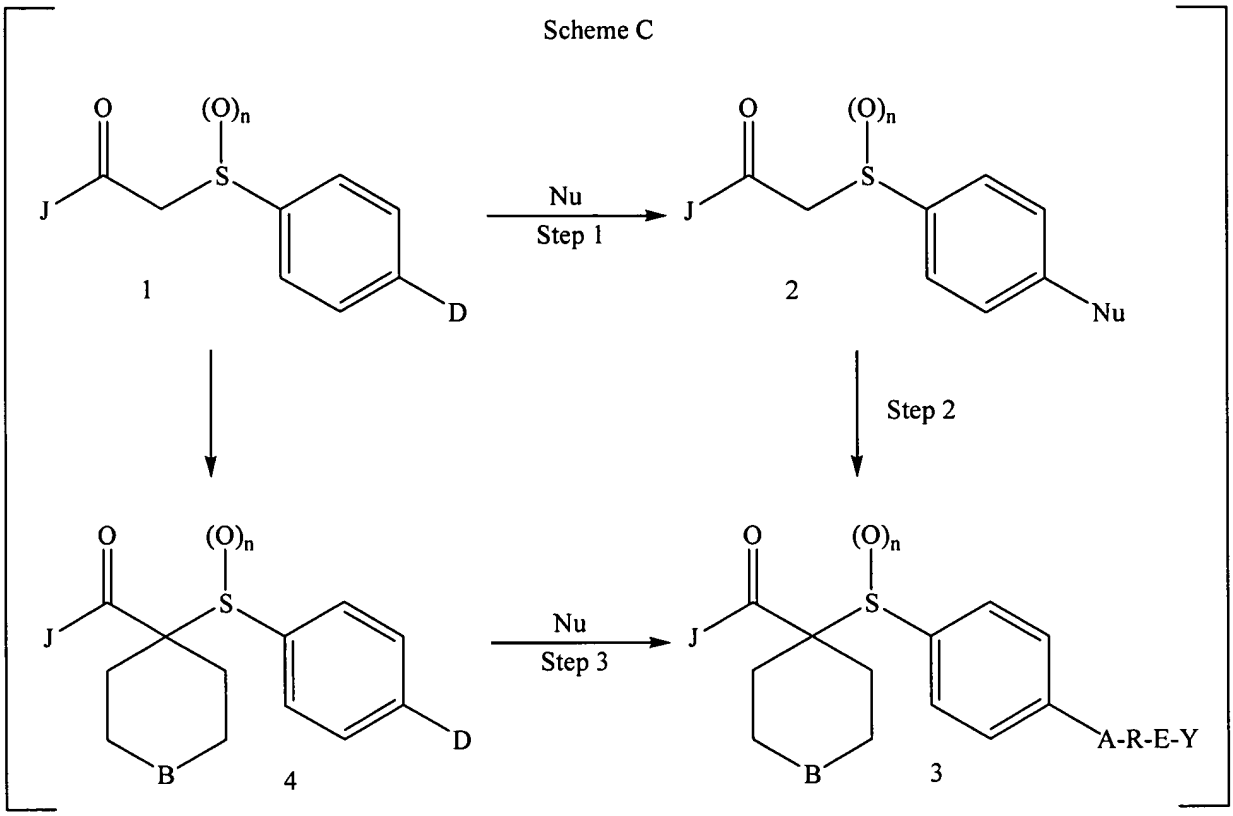


Scheme B

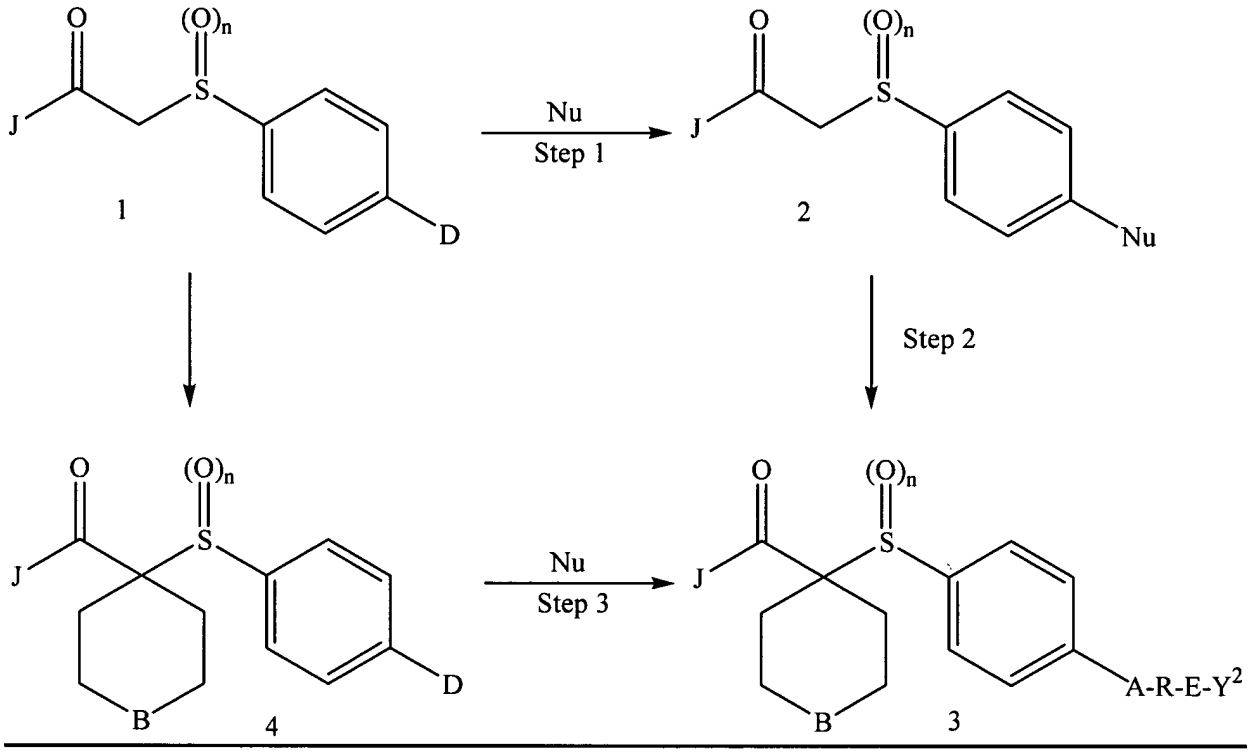


**Scheme C at line 17 on page 103 has been amended as follows:**

Scheme C



Scheme C




**The paragraph bridging lines 13-18 on page 104 has been amended as follows:**

Steps 1, 2 and 3 also illustrate that although the nucleophilic displacement can be carried out with one nucleophile (Nu), the product of this reaction can be modified by methods well known in the art and as shown herein to provide the group -A-R-E-$Y^{\underline{2}}$ as defined hereinbefore.

**The paragraph bridging lines 19-31 on page 104 has been amended as follows:**

A non-limiting illustration of such a process is provided when D is fluoride. The fluoride leaving group can be directly displaced with the anion of 4-trifluoromethylphenol, 4-trifluoromethoxyphenol, 4-trifluoromethylthiophenol and the like to provide a contemplated compound. This is a one pot process from Compound 4. Other compounds included in -A-R-E-$Y^{\underline{2}}$ can be prepared by displacing the fluoride leaving group with ammonia to provide an amine, which can then be acylated by methods discussed wherein with, for example, 4-trifluoromethylbenzoyl chloride, to form another contemplated product compound.

**The paragraph bridging pages 870 and 871 (*i.e.*, page 870, line 25 to page 871, line 16) has been amended as follows:**

MMP-1 expressed in transfected HT-1080 cells was provided by Dr. Harold Welgus of Washington University, St. Louis, MO. The enzyme was also activated using APMA and was then purified over a hydroxamic acid column. Dr. Welgus also provided transfected HT-1080 cells that expressed MMP-9. Transfected cells that expressed MMP-2 were provided by Dr. Gregory Goldberg, also of Washington University. Studies carried out using MMP-2 in the presence of 0.02% 2-mercaptoethanol are shown in the table below with an asterisk. Studies with MMP-7 were carried out at pH 7.5 in the presence of 0.02% 2-mercaptoethanol using conditions otherwise similar to those used for the other enzymes. The enzyme was obtained from a hMMP-7 expressing E. coli clone that was a gift of Dr. Steven Shapiro of Washington University, St. Louis, MO. Further specifics for preparation and use of these enzymes can be found in scientific literature describing these enzymes. See, for example, Enzyme Nomenclature, Academic Press, San Diego, CA (1992) and the citations therein, and **[[Frije]] Freije** et al., J. Biol. Chem., **[[26(24)]] 269(24)**: 16766-16773 (1994). The enzyme substrate is a methoxycoumarin-containing polypeptide having the following sequence:

**The paragraph bridging lines 8-15 on page 880 has been amended as follows:**

The study of angiogenesis depends on a reliable and reproducible model for the stimulation and inhibition of a neovascular response. The corneal micropocket assay provides such a model of angiogenesis in the cornea of a mouse. *See*, ~~***A Model of Angiogenesis in the Mouse Cornea*; Kenyon, BM, et al., Investigative Ophthalmology & Visual Science,***~~ **Kenyon, B.M., et al., "A Model of Angiogenesis in the Mouse Cornea", *Investigative Ophthalmology & Visual Science*, Vol. 37, No. 8, pp. 1625-32** (July 1996) ~~**, Vol. 37, No. 8**~~.

**CERTIFICATE OF MAILING UNDER 37 CFR §1.8**

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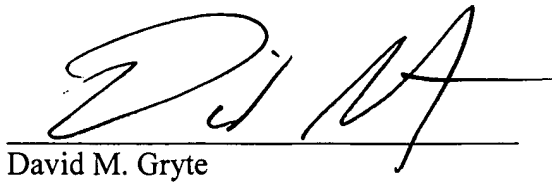

David M. Gryte

DMG/LNN/PML